PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/002421	07.06.2004	06.06.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/861, C07K7/06, A61K48/00

Applicant
ICH PRODUCTIONS LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/002421

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1(partially), 16-29, 30-107(partially), 108

because:

☒ the said international application, or the said claims Nos. 97,99-101,108 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1(in part), 16-29, 30-107(in part), 108

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1 (partially), 2-15, 30-107 (partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-15,30-107
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-15,30-107
Industrial applicability (IA)	Yes:	Claims	1-15,30-96,98,102-107
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/002421

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

N.1 Claims 97, 99-101 and 108 relate to methods of treatments of the human/animal body, which are considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

N.2 The International Search Authority has found that the present application relates to separate inventions or groups of inventions. As no additional search fee has been paid, only the subject-matter relating to the invention first mentioned in the claims has been searched (see point U.4[a] below). The examination will be limited accordingly (Rule 66.1(e) PCT). The subject-matter of claims 1 and 30-107 is therefore examined in so far as the claims only relate to peptides comprising the motif of Seq. ID 1. The subject-matter of claims 16-29 and 108 is not examined because these claims do not relate to said peptide motif.

Re Item IV

Lack of unity of invention

U. UNITY (Rule 13(1) PCT).

U.1 The present application concerns drug delivery systems for nucleic acid-containing drugs.

U.1[a] The general idea of a nucleic acid-based therapeutic approach is clearly not novel over gene therapy, antisense therapy and nucleic acid vaccination (see for example points 1.9 and 1.10 below).

U.1[b] No further common concept is present between the subject-matter of claims 1-107 and the method of claim 108. Claims 1-107 concerns peptides for targeting nucleic acid-containing drugs to the patient cells in order to improve the delivery of the active agent, whereas claim 108 relates to the identification of further siRNA moieties as the active agents and does not refer to any targeting peptide.

U.1[c] Hence, no common inventive concept is therefore present between the peptides of claims 1-107 and the method of claim 108, and a lack of unity "a posteriori" is

indicated.

U.2 The common concept, which would link the peptides of claim 1 together, is the idea of using peptidic moieties, other than naturally occurring full length proteins, for targeting nucleic acid-containing drugs to the therapeutically relevant cells.

U.2[a] This idea is not novel because the prior art describes the targeted delivery of nucleic acid vectors into mammalian cells by means of artificial proteins (e.g. mutated proteins and chimeric proteins) and targeting peptides (see for example points 1.1-1.2 and 1.9-1.12 below).

U.2[b] Hence, the common concept identified above cannot be considered a single general inventive concept according to Rule 13(1) PCT, and the lack of unity "a posteriori" applies also to the different peptide motifs of claim 1.

U.3 As described in the present application, exemplary peptides according to the definition of claim 1 have been identified by screening peptide libraries against dendritic cells.

U.3[a] This screening method and the dendritic cell-binding property of the peptides do not represent common inventive concepts for the purpose of unity of invention because the prior art discloses screening methods for the identification of vector-targeting peptides and indicates dendritic cells among the preferred targets of nucleic acid-containing drugs (see for example points 1.1 and 1.10-1.12 below). In particular, D12 discloses a fusion protein for targeting viral vectors to dendritic cells, wherein the amino acid sequence of the protein comprises one of the peptidic motifs of claim 1 (see point 1.12 below).

U.3[b] In addition, the dendritic cell binding property is not an exclusive feature of the claimed peptides because peptides according to the definition of claim 1 are known as targeting agents for cells other than the dendritic cells of the present application (see for example points 1.3-1.5 below).

U.4 Having regards to:
(i) the prior art,
(ii) the different peptide motifs of claim 1, and
(iii) the subject of claim 108,

there is no single technical relationship among the claimed subject-matter involving one or more of the technical features to which an inventive step can be addressed.

The four different peptide motifs of claim 1 and the method of claim 108 represents therefore five separate inventions (see below), none of which is linked

with any of the others as to form a single general inventive concept.

U.4[a] Subject 1: claims 1 (partially), 2-15, 30-107 (partially).
Peptides comprising the motif of Seq. ID 1 (i.e. PXXXT), compositions and medical uses thereof, as well as antibodies and methods for producing said compositions: transfection mixtures, complexes, vectors, kits,...

U.4[b] Subject 2: claims 1 (partially), 16-20, 30-107 (partially).
Peptides comprising the motif of Seq. ID 2 (i.e. PSXS), compositions and medical uses thereof, as well as antibodies and methods for producing said compositions: transfection mixtures, complexes, vectors, kits,...

U.4[c] Subject 3: claims 1 (partially), 21-25, 30-107 (partially).
Peptides comprising the motif of Seq. ID 3 (i.e. QXXXQ), compositions and medical uses thereof, as well as antibodies and methods for producing said compositions: transfection mixtures, complexes, vectors, kits,...

U.4[d] Subject 4: claims 1 (partially), 26-29, 30-107 (partially).
Peptides comprising the motif of Seq. ID 4 (i.e. SXS), compositions and medical uses thereof, as well as antibodies and methods for producing said compositions: transfection mixtures, complexes, vectors, kits,...

U.4[e] Subject 5: claim 108.
Method for the identification of siRNAs.

U.5 The present examination has been carried out only for Subject 1 (see point N.2 above). Hence, any reference to claims 1 and 30-107 below concerns only the subject-matter of this searched/examined invention.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. DOCUMENTS and ABBREVIATIONS.

X is hereafter used as to mean a generic amino acid residue.

Reference is made to the following documents:

D1: Ivanenkov V. V. et Al., *Biochimica Et Biophysica Acta* (1999) Vol. 1448, No. 3, Pages 463-472;
D2: WO 98/44121 A;
D3: WO 02/057445 A;
D4: WO 03/004646 A;
D5: DE 198 45 251 A;
D6: Boer J. et Al., *Journal of Medicinal Chemistry* (2001) Vol. 44, Pages 2586-2592;
D7: WO 03/008537 A;
D8: WO 91/18010 A;
D9: WO 98/54347 A;
D10: WO 02/072616 A;
D11: WO 01/58940 A;
D12: Pereboev A. V. et Al., *Gene Therapy* (2002) Vol. 9, No. 17, Pages 1189-1193.

1.1 D1 discloses peptide ligands for targeting transfection vectors, like gene complexes and viruses (see abstract and lines 3-6 of the right-hand column on page 463). The targeting peptides have been identified by screening phage-display libraries against HEp-2 and ECV304 cells (see abstract). One of the peptide thereby identified is IYPSYGTTL (see table 1, third peptide).

1.2 D2 discloses mutated adenovirus fibre proteins for targeting viral vectors of therapeutic interest to the desired cells (see: abstract; paragraph joining pages 4 and 5; page 10, lines 14-17; claims 3,6-8,29,33-34). In particular, the mutated proteins comprise the peptidic motif PPLTT (see Seq. ID 1).

1.3 D3, D4 and D5 discloses targeting peptides for drug delivery (see: D3, abstract

and claims 44-47; D4, abstract and table 4; D5, abstract). In particular, vectors for gene therapy and DNA vaccines are indicated as drug moieties to be targeted (see: D3, claim 44; D4, abstract; D5, page 2, lines 21-29). Short peptides of 7-17 amino acid residues are specifically discloses in these documents. These peptides comprise the motifs PQLIT, PVNFT, PRLLT and PGRPT (see: D3, table 1, Seq. IDs 61 and 82; D4, table 4, the 29th peptide on page 50; D5 Seq. IDs 1, 39 and 40 on pages 6-7). The peptides of D3 and D5 have been identified by screening peptide libraries against cells of interest (see the abstracts).

1.6 D6 discloses cyclic peptides as integrin antagonists (see abstract). In view of the cyclic structure, the peptides cyclo(LDTXpX) and cyclo(LDTpA) comprise the peptidic motif pXLDT (see tables 1 and 2).

1.7 D7 discloses peptide epitopes for anticancer vaccines (see abstract). Some of these peptides are 8-10 amino acids in length and comprise the sequence PSLYT or PKAYTV (see table 1C, Seq. IDs 393, 394, 398, 399, 537, 538).

1.8 D8 discloses intercellular adhesion molecule-1-like peptides for inhibiting viral infections, e.g. PGNWT (see the abstract and the fourth peptide of table 2).

1.9 D9 discloses transfection vectors for gene/antisense therapy and DNA vaccination comprising integrin-binding peptides for targeted delivery (see: abstract; claim 47; from line 22 on page 5 to line 15 on page 10).

1.10 D10 discloses non-viral and viral transfection vectors, which comprise targeting peptides, for gene therapy, antisense therapy and DNA vaccination (see abstract and claims 21-81). The targeting peptides have been identified by screening peptide libraries against human airway epithelial cells (see: page 5, lines 2-7; examples 1-2).

1.11 D11 discloses viral vectors with a modified adenoviral protein domain, which consists of a chimeric pIX protein comprising a cell-specific targeting ligand, eventually selected by screening peptide libraries for the desired interaction (see: abstract; example 1; paragraph joining pages 6 and 7). Dendritic cells are mentioned among the target cells (see: page 5, first paragraph; page 6, second paragraph).

1.12 D12 discloses a fusion protein for inducing the transfection of dendritic cells by adenoviral vectors (see abstract). The fusion protein is specifically targeted to dendritic cell by means of the relevant fragment of an anti CD40 antibody and comprises a peptidic linker of sequence PSASASASAPGS (see figure 1).

2. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT.

2.1 For the assessment of the present claims 97, 99-101 and 108 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. Methods for the identification of therapeutically active compounds, like present claim 108, are also to be considered as relating to a method of treatment in so far as the method can be carried out in-vivo.

2.2 Claims 1-15, 30-96, 98 and 102-107 relate to drug targeting peptides, antibodies thereto, drug delivery systems, methods and kits for their preparation, and their use for the preparation of pharmaceutical compositions. Said peptides, antibodies, drug delivery systems, kits, methods and uses can be made or applied in the pharmaceutical industry, hence they are to be considered industrially applicable according to article 33(4) PCT.

3. NOVELTY (Art. 33(2) PCT) and INVENTIVE STEP (Art. 33(3) PCT).

3.1 The subject-matter of claim 1 is not novel because the prior art discloses peptides and proteins, other than naturally-occurring full length proteins, comprising the motif PXXXT (see points 1.1-1.8 above).

3.1[a] In particular, the cyclic peptides of D6 are to be considered as falling within the claimed scope because capital single letter codes are also used in the current practice to indicate amino acid residues, irrespective of the enantiomer configuration of the α-carbon atom. Hence, the reference to the "P" amino acid residue in present claim 1 is considered to include both (L)-Pro and (D)-Pro

residues. The present application does not explicitly limit the meaning of capital single letter codes for amino acids to the (L) enantiomers.

3.2 Dependent claims 2-15, 30-46 and claims 47-107 do not contain any features which, in combination with the peptide features of claim 1 to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step because the prior art also discloses the medical uses of the peptides falling within the scope of claim 1 (see points 1.1-1.5 and 1.7-1.8 above). In particular, most of these disclosures concerns the use of these peptides as targeting agents for nucleic acid-containing drugs (see points 1.1-1.5 above).

3.2[a] In addition, D10 discloses targeting peptides for nucleic acid drug delivery (see point 1.10 above). Apart from the different peptidic motif, these peptides and the corresponding transfection complexes and mixtures, which are also disclosed in this document, have technical features according to the preferred embodiments of the present application. The skilled person would have considered to incorporate these additional technical features in the targeting peptides and the transfection vectors disclosed/suggested in any of D1-D5.

3.3 Independently from the reasoning above, the subject-matter of claim 1 does not involve any inventive step over D9, taken in combination with D6.

3.3[a] D9 discloses nucleic acid drug delivery systems and their targeting peptides, which differ from the subject-matter of independent claims 1, 51, 65, 79 and 80 in the amino acid sequence of the targeting peptides (see point 1.9 above).

3.3[b] The problem can therefore be regarded as the provision of further targeting peptides for nucleic acid drug delivery systems.

3.3[c] As the integrin binding activity is the biologically relevant property of the targeting peptides of D9, the skilled person would have considered the peptides disclosed in D6 in order to solve the problem posed, thereby obtaining peptides and transfection systems according to the present application (see point 1.6 and 3.1[a] above). Integrin binding is an inherent property of the integrin antagonists of D6 (see the paragraph joining the left- and the right-hand columns on page 2586 of this document).

3.3[d] Dependent claims 2-15, 30-46, 52-63, 66-75 and claims 47-50, 64, 76-78, 82-83, 97-107 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, given the disclosure of the prior art.

Re Item VIII

Certain observations on the international application

C. CLARITY (Art. 6 PCT).

C.1 Although claims 1, 47, 51, 64, 65, 76, 78, 79, 80, 82, 83, 84, 97-108 have been drafted as separate independent claims, most of them effectively relate to (define) the same subject-matter and differ from each other only in respect of the terminology used and/or in the definition of the preferred features. For example, claims 79 and 83 attempts respectively to define the same transfection complexes of claims 65 and 80 in terms of the process for their preparation. The subject-matter of claim 47 falls within the scope of independent claim 1, and claim 47 is equivalent to dependent claim 42. The complex of claim 65 is a preferred embodiment of the complex of claim 80 in view of the additional lipid component. A similar observation applies to the kits of claims 105 and 106 and the processes of claims 76, 78 and 82. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

C.1[a] In particular, claims 79 and 83 attempt to define a product in terms of the process by means of which the product can be obtained. As the process itself is merely defined in terms of the product to be produced, claims 79 and 83 are redundant and do not introduce any further relevant product feature.

C.2 A claim referring to negative features (i.e. proviso) cannot be considered as providing a clear definition, if other conditions can release the constrains set by these negative features. In the present case, claim 1 excludes full length natural proteins from the claimed scope, whereas some of the dependent claims (e.g. claim 35) cancel this exclusion while introducing additional independent features. The reader is therefore confused about the technical features, which effectively characterize the claimed subject-matter. Moreover, a dependent claim should contain all the essential features referred to in the corresponding independent claim (see the PCT Guidelines 5.15).

C.3 The term "variant" used, for example, in claim 29 is vague and leaves the reader in doubt as to the meaning of the technical feature to which it refers, i.e. the effective peptide sequence, thereby rendering the definition of the subject-matter of said claims unclear. As there is no upper limit for the number of terminal residues which can be omitted, dipeptides could also be considered to fall within